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Development of Provenge for Prostate Carcinoma Therapy

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Abstract. Provenge, as an autologous cell immunotherapy agent, was originally used to stimulate the immune cells and immunologic factors to destroy prostate cancinoma cells. For patients with hormone resistant metastatic ovarian cancer, when there are no clinical symptoms, compared to the placebo arm, the drug arm can effectively extend the median survival period of four point one months. During the three years of treatment, more than 50% of patients in the immunotherapy arm survived, and more than 50% of patients in the control group survived (31.7% vs 21.7%). Provenge, targeted to release prostate acid phosphatase, utilizes the patient's immune cells to detect and eliminate tumor cells. At the moment, there are not useful therapeutic strategies for asymptomatic patients without docetaxel and other chemical drugs treatment. The direct strategy to increase the effectiveness of Provenge is to promote more effective clinical benefits. Although the preclinical analysis and clinical efficacy of Provenge have been summarized, the clinical efficacy of enhancing efficacy needs to be reconsidered.

Keywords: provenge, Ovarian cancer, immunotherapy

1. Introduction

In western countries, prostate carcinoma is the second capital reason of death for men, with 34500 deaths in USA in 2022[1]. The initial therapy of prostate carcinoma depends partly on the patient's age, the growth rate of tumor cells, and other prognostic factors. Active immune surveillance is not the first choice for patients with local tumors. Surgery or radiotherapy can cure the patients. However, as high as 30% of patients will relapse, which is usually manifested by progressive increase of prostate specific protein in patients' serum. Although the recurrence of prostate carcinoma can be controlled by hormone therapy, this disease will unavoidably develop into metastatic androgen tolerant prostate carcinoma [2]. The traditional treatment for prostate carcinoma patients with metastatic androgen resistant is chemotherapy (docetaxel) or second-line treatment hormone therapy, and ultimately, hospice care (palliative treatment). For these patients, tumor specific immunotherapy can promote adaptive anti-tumor response with low toxicity and high effectiveness. Although many methods lead to an immune response against tumor antigens, until recently, the survival benefits of patients have evolved from elusive to clear.

In 2010, the FDA approved Provenge therapy of asymptomatic prostate carcinoma. As a therapeutic vaccine, Sipuleucel-T can activate the immune response against prostate carcinoma cells and target prostate acid phosphatase [3]. Its therapeutic aim is to produce specific T cells targeting prostate acid phosphatase, which can recognize and destroy prostate carcinoma cells overexpressing prostate acid phosphatase. After prostate cancer surgery, the tissues that retain the expression of prostate acid phosphatase are mainly prostate cancer tissues. The prostate acid phosphatase vaccine

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antigen is composed of PA2021, which is a recombinant protein that fuses the expression of prostate acid phosphatase and granulocyte-macrophage colony-stimulation factor (GM-CSF). The recombinant protein was co-incubated with PBMC. Human GM-CSF is used to activate antigen presenting cells [4]. Activated antigen presenting cells can activate and induce the proliferation of PAP specific T cells to distinguish and kill PAP-overexpressing prostate carcinoma cells. 96 hours after monocytes were collected and incubated for 40 hours, the immune cells were washed to eliminate the recombinant protein, and then transported to the patient care center, where Sipuleucel-T products were infused into the patients.

Although Provenge was marketed in 2010, the article on the complete research and development process of the preclinical research, phase I clinical studies, phase II clinical studies and phase III clinical studies of Sipuleucel-T has not been published [5]. This article reviews Provenge's preclinical studies, Phase I and Phase II clinical studies, Phase III clinical studies, and Phase IV clinical studies.

2. Preclinical studies

Prostate gland varies extremely due to different species and immune system. Therefore, the test results of prostate cancer animal models can not immediately reflect the test of prostate carcinoma vaccine in prostate cancer patients. However, previous research has illustrated that scientists immunized rat with rat prostate specific antigen, which can lead to destructive prostatitis [6]. Antigen presenting cells incubated with rat PAP and GM-CSF can cause prostatitis [7], but will not produce toxicity to normal nonprostate tissues. These trials suggest that this treatment may break through immune tolerance and lead to autoimmunity against prostate tissue [8]. Although prostate gland cannot be completely damaged by PAP vaccine, even if autoimmune prostatitis occurs, prostatitis caused by dendritic cell vaccine has laid a foundation for this similar vaccine against prostate cancer.

The high tissue specificity of the treatment is mainly reflected in the fact that the immune cells only infiltrate in the prostate tissue, which indicates that the treatment scheme breaks through the tolerance of self-antigen and the effective participation of adaptive immunity in the immune system. It is worth noting that when the antigen presenting cells or GM-CSF protein in the preparation are removed, the therapeutic response will be weakened. This experiment shows that three preparation components (antigen presenting cells, GM-CSF and target antigens) are essential for generating intense T cell responses. Other preclinical experiments showed that the proliferation of tumor cells was inhibited when PAP overexpressing cancer cells were co-cultured with animal spleen cells immunized with PAP-GM-CSF [9].

3. Phase II clinical Trials

In 2004, Professor Burch and his colleagues recruited 21 hormone independent prostate cancer patients and completed the Phase II clinical trial. APC8015 is from the cell collection device. It includes antigen presenting cells stimulated by autologous CD54 positive PA2024, mixed with monocytes, macrophages, T and B cells. APC8015 is sent back twice with an interval of 14 days. 14 days after the second reinfusion, the patient received three s.c injections of GM-CSF-PAP, 1.0mg each time, with an interval of 1 month. We monitor patients' physiological conditions, immune responses and laboratory indicators. Nineteen patients evoked an immune response to therapy. The median survival time for progression was 118 days. The patient has a good tolerance to the treatment, and the most common side effect is that the second time of APC8015 reinfusion produces 1-2 grade toxic side effects. Four of the twenty-one patients had grade 3-4 side effects. Two patients showed a transient reduction of 25-50% against PSA. In 1/3 of the patients, the PSA level decreased from 221ng/ml to below the detection level at 24 weeks, and maintained for more than four years. Besides, one patient developed retroperitoneal metastasis and was cured of pelvic adenosis. Peripheral blood mononuclear cells collected in patients proliferated at least 16 weeks after PA2024 stimulation in vitro. In patients who responded to treatment, peripheral blood mononuclear cells were excited for 96 weeks. This trial illustrates the clear clinical response of hormone independent prostate carcinoma needle to antigen presenting cell immunotherapy [12].

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4. Phase III clinical Trials

Two phase III clinical trials (D9901 and D9902A) were initiated to treat prostate carcinoma and accelerated FDA approval of the drug. Both trials were placebo-controlled, double-blind, randomized trials involving asymptomatic patients who were suffered from metastatic prostate cancer. The initial node is the median time to observe the disease progression, and the second node is the planned overall survival.

In the control group, autologous PBMCs were enriched from blood cells, but PA2024 was not incubated in the process of PBMC culture (for example, GM-CSF without antigen or with activation effect). Only 1/3 of the blood cells were collected for the control sample preparation procedure. The remaining peripheral blood monocytes are frozen and may be used in the planned rescue vaccine research.

For the D9901 study, the median period of disease progression in the Provenge group was 11.7 weeks, and the median period of disease progression in the control group was 10 weeks. The curve separates at week 8, and the separation lasts for the whole process. However, between the two groups there was no significant difference (P=0.052). The median total survival time of Sipuleucel-T arm was 112 weeks, compared to the control arm's 93 weeks. The total survival time of Sipuleucel-T group increased by 4.5 weeks and was statistically significant (P=0.01).

The discrepancy between the positive results of the overall survival and the median survival time of disease progression shows that it may not be appropriate to use the median survival time of disease progression as a measurement method to measure the vaccine effect in prostate cancer patients with very short disease progression. Because the treatment scheme requires 3 doses of vaccine, the subject may not have the optimal immune response until after the third immunization (for example, after 4 weeks of immunization). The median period of disease progression is ten to eleven weeks, and the optimal immune response will occur 6-7 weeks before the disease progression is observed. This time may be too short to be observed in time to prolong the progress time, although the final results show that the vaccine leads to an extended median survival. What's more, it is very difficult to accurately detect cancer progression in prostate cancinoma patients. Bone scans' new lesions may be considered as disease progression, even if there is a reaction to the disease in the patient's body (such as shining phenomenon). Combining PSA level rise with bone scan progression in the opposite direction may wrongly lead to appointment as disease progression. Based on the results of this experiment and other immunotherapies, the Second Working Group on Prostate Cancer recently revised the disease development guidelines to avoid the phenoma.

In the second phase III study D9902A, there was no statistical difference in the time of disease progression. The median survival period of Sipuleucel-T group was longer than that of the control group (15.7 months vs 9.0 months), and the 3-year survival rate was increased by 50% (32.3% vs 21.2%). Although the overall 3-year survival period benefited significantly, there was no statistically significant difference in prolonging the median survival period (P=0.031). The median time of disease progression usually occurred in the sixth week after the third vaccination, and before the median survival time of one year.

D9902B (another name was the IMPACT trial), which is the third phase III clinical trial, accelerated FDA approval of the drug for marketing. Its initial node is the total lifetime. IMPACT is a placebo-controlled, double-blind study, which is related to 512 asymptomatic or least symptomatic patients with mCRPC. The 512 prostate cancinoma patients were randomly divided into Sipuleucel (n=341) and control (n=171) groups according to 2:1. Provenge arm was treated once every two weeks, three times in total. 330 patients received Provenge treatment, 92% received 3 times of reinfusion, and 93% of the control group received 3 times of reinfusion. Compared with the control arm, the median survival time of the treatment arm was 25.8 months, and that of the control group was 21.7 months. (P=0.032), the median survival benefit was 4.1 months. The adjusted mortality risk ratio (HR) was 0.78. The KM parameter was 31.7% in the treatment arm and 23.0% in the control arm when it took 36 months, indicating that the overall survival rate within 3 years was increased by 38%.

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These clinical trial results are identical to the clinical data collected during the Phase I studies and Phase II clinical studies, the results of pre-clinical rat studies, and the characteristics of the product, which is conducive to understanding the mechanism of the cell product. In particular, PAP-GM-CSF protein is absorbed by large volume of CD54+, MHCII+ antigen presenting cells; Antigen presenting cells were activated by culture medium; The medium can up regulate CD54, MHC II and other molecules; Antigen presenting cells present PAP epitopes to PAP specific T cells in a MHC II restricted manner. The increase of CD54 protein in antigen presenting cells was related to the total survival period, which showed that the immune response was initiated after the first dose of administration, and the memory immune response pattern was generated after the 2nd and 3rd doses of reinfusion of dendritic cells. Provenge is an autologous cell therapy preparation, which is composed of PBMC, including antigen presenting cells. Recent studies have confirmed that other cells in this preparation are not passive bystanders, but actively participate in defining product characteristics. For example, when preparing the second or third cell preparation for T cytokines such as interleukin 2, IFNR, IL-17, compared with the first cell preparation, the cytokine in the culture medium is at least 50 times higher. This phenomenon further indicates that the immune response of patients is initiated when cells are returned for the first time, and the T cell components involved can be detected when preparing the second and third preparations. The activation of NK cells was consistent with the composition of the culture medium during the second preparation of the cell preparation (interestingly, this scenario was not seen during the first and third preparation of the cell preparation). This indicates that both adaptive immunity and innate immunity are involved in the preparation and three times of reinfusion of Provenge.

5. Phase IV clinical Ttrials

In 2019, Professor Higano and his colleagues completed the Phase IV clinical trial. The large registry, PROCEED (NCT01306890), evaluated the immunotherapeutic effect of Provenge on prostate cancer patients. Between 2011 and 2017, 1976 patients were interviewed randomly for 46.6 months. PROCEED institution provided survival data of Sipuleucel-T treatment group in the same period. This study will discuss the therapy strategies of patients and future study on Provenge. The safety and tolerance tests of Provenge in PROCEED institutions are in accordance with previous findings [13].

In 2022, Professor Xiao and his colleagues reviewed the therapy strategies of 1902 prostate carcinoma patients in PROCEED and the continuous Provenge treatment of 255 patients in DFCI between April 2010 and April 2017. 171 patients and 28 patients were selected from the two institutions respectively. Using these two databases, we analyzed prostate cancer patients using Sipuleucel-T. When they did not immediately start the next treatment, the level of PSA response showed a delayed change, indicating that Sipuleucel-T had delayed clinical activity.

In addition to proposing an acute reinfusion response analysis, FDA supports a comprehensive safety analysis and this safety analysis is submitted to the Biolicense application [14]. The package inserts are not helpful to the prescription doctor. The comprehensive safety analysis was based on 601 prostate cancer patients experienced at least one leukocyte isolation process, which included 4 random control trials [D9902A, P-11, and D9902B]. The comprehensive safety analysis shows that adverse events will occur throughout the research and development period. Therefore, continuous but uncertain adverse events occurred after cell reinfusion, and were comparable to the control group in the cell therapy group, which strongly proved that the occurrence of adverse events was due to diseases, not cell agents.

The incidence of cerebrovascular disease events in Provenge treatment group was 2.4%, while that in control group was 1.8%. Since most of the side reaction occurred half a year after the last cell reinfusion, the importance of cell reinfusion remains unclear. At present, FDA is requesting to provide after-sales registration of 1500 patients after marketing to further confirm the risk of cerebrovascular disease.

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6. Conclusion

Prostate cancer is a common cause of death in men. Patients can be cured by conventional surgery or radiotherapy. However, up to 30% of patients relapse. Tumor Hapten therapy is a new approach in recent years. It has low toxicity and high efficiency. Treatment of prostate cancer with Provenge can improve the overall survival period of patients, while producing mild and short-lived side effects. The usual treatment mode is to activate cellular immunity when cells are reinfused for the first time, and enhance cellular immunity effect when cells are reinfused for the second time. This treatment regimen can lead to strong and lasting immune responses which specifically targets the fusion protein PA2024. The treatment of tumor seems to be immunotherapy, but its application is still limited. Future research and treatment feedback remain the focus.

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